Type-2 Diabetes: Abnormalities associated with the elevation in level of liver function tests (LFTs)

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ABSTRACT

Liver Function Test (LFTs) is very common for the primary analysis of any types of malfunction associated with liver. For screening of liver in clinical practice, widely used LFT includes- ALT (*alanine amino transferase*), AST (*aspartate amino transferase)*, Alkaline Phosphate (AP), Bilirubin, Albumin and Prothrombin Time (PT). In type-2 diabetic patients, a nonspecific Gamma-Glutamyl Transferase (GGT) marker is increased. While analyzing the epidemiological studies, intake of alcohol, cigarette smoking, BMI, Systological Blood Pressure, Coronary Heart disease, Heart Rate, hematocrit, uric acid it having the positive association. But at the same time it shows the inverse effect with the physical activities. GGT is proposed as another marker for insulin resistance because the GGT increases in diabetes. It is concluded that the individuals who have type-2 diabetes seems to have higher incidence of LFT abnormalities than the person who are not diabetic. For more than 6 months, elevation of ALT is commonly observed. It develops a mild chronic elevation & it should be screened for treatable cause of chronic liver disease like in hepatitis-B and C. Patients having regular monitoring generally donot observe any elevation in level of LFTs. Before starting any oral anti-diabetic or lipid modifying therapy, a proper clinical judgment should be required. Elevation of *transaminase* not always correlated with histological changes in liver. But at the same time a fall in level of ALT is achieved in blood while giving anti-diabetic agent to patients.

Keywords: LFT, Antidiaibetic, Drug therapy, lipid modifying therapy.

INTRODUCTION

Liver function test (LFTs or LFs) also called as hepatic panel; it gives us the information at clinical level by proper routine diagnosis of blood serum of patient's liver. A proper monitoring should required for the earlier detection of any malfunction associated with the liver. Type-2 diabetes Mellitus (T2DM) is a chronic, progressive and serious metabolic disorder

characterised by hyperglycaemic disorder (high blood glucose levels) & associated with numerous complication & co-morbidities, including cardiovascular disease, nephropathy (kidney damage), neuropathy (nerve damage) & retinopathy (retinal damage). Global prevalence of the disease has risen rapidly in the past several decades, primarily as a result of rising obesity a major risk factor for T2DM. Commonly perform LFTs which are serum aminotransferases, alkaline phosphatase, bilirubin, albumin & prothrombin time. Aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which act as maker for hepatocyte injuries and it measure the concentration of intracellular hepatic enzymes. It leaked out during blood circulation for billiard functions and cholestasis. Alkaline phosphatase (AP), μ-glutamyl transpep- tidase (GGT), and bilirubin act as marker and for the synthetic function albumin & prothrombin are responsible. The amino transferase AST and ALT are normally range for < 30-40 units/l. An acute viral hepatitis, ischemic hepatitis drugs-or-toxin induced liver injury when the normal upper ranged limit is greater by 8 times. A chronic mild elevation of aminotransferases, or AST and ALT< 250 units/l for >6 months are much more common among the patients with acute hepatitis.

This article will provide us a review on the clinicopathological investigation related to the incidence, causes and drug therapy which associated with the type 2 diabetic patients along with their elevated LFTs level. In type 2 diabetic patients a chronic mild elevation of transaminases are found generally.

LFTs Elevated in type-2 Diabetes

During fasting & postpraudrial state, liver help to maintain the normal blood glucose concentration. A reduction of insulin level in liver it increases the glycogenolysis & hepatic glucose production. Liver externalised the conditions which depict by the insulin resistance & are distinguishable earlier than fasting hyperglycaemic. The triglyceride storage & lypolysis abnormalities found in liver which is an insulin- sensitive tissue. However, it is unequivocal that the methodical genetic events, environmental, metabolic factor & sequence of the events lead to the cardinal insulin resistance [1].

Chronic hyperinsulinemia is found to be more liable towards the liver relative resistance of insulin for the animal models.

This signalised the failure of insulin signal by increasing the insulin receptor substrate-2. The process of lipogenesis is increased by the up gradation of sterol regulatory element-binding protein 1c (SREBP-1c) [2]. Promoting the fatty liver & increase the triglycerides availability by the de novo lipogenesis in the liver responsible for the regulation of SREBP-1c. Hence, down the regulation of insulin receptor substrate-2-mediated insulin signalling pathway in insulin resistance states. As the VLDL assembly & secretion also increased [1].

Automatically it becomes toxic for hepatocytes when the excess of free fatty acids found in the insulin-resistance state. The keys processes involved in the regulation of metabolism the eminent mechanisms which include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, activation and inhibition [3]. Other feasible interpretation for elevated transanimases in insulin-resistance states which involve the oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation and recruited inflammatory cells. The insulin- resistance state is delineate by an increased increase in proinflammatory cytokinesis such as tumor necrosis factor-a (TNF-a), and marked the hepatocellular injury. In primary stage studies, it propound a possible genetic link or inclination to fatty liver as the increased frequency of specific TNF-a–promoter polymorphism was found in nonalcoholic steato-hepatitis (NASH) patients [4]. All the above theories allege elevated transamination to direct hepatocyte injury. The impairment in insulin signaling rather than purely hepatocyte injury which is marked by gluconeognesic enzymes whose transcription is suppressed by insulin and it also hypothesized the elevation in ALT level [5].

Elevated LFTs can Prolongate Diabetes?

In type-2 diabetic patients a non-specific marker GGT level is increased. In epidermiological studies, it association is positive with cigarette smoking , alcohol intake, heart rate, BMI, systolic blood pressure, coronary heart disease, serum triglyceride, uric acid & hematocrit. It has a direct involvement with the physical activities [6]. As GGT level rise in diabetes & it results increased in BMI. Hence, it has been introduce as another marker of insulin resistance. A prospective cohort study of 7458 non-diabetic men aged 40-59 years was conducted for 12 years. It helps to evaluate the GGT which predict the development of type-2 diabetes while predicting a model as the GGT was added,

but there is no process of progress reported in BMI strength and glucose for antipating the development of type-2 diabetes.

In non-diabetic Ohlson et al found ALT a risk factor develop for type-2 diabetes swidish men, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentraction & family history of diabetes [8].

Same result found, Vozaroza et al it took 451 non-diabetic Pima Indians for approximate 6.9 years it allocate whether the development of type-2- diabetic linked by the hepatic enzyme elevations [9].

Percent body fat related to baseline of ALT, AST and GGT elevated ALT at baseline associated with the increased in hepatic glucose output. Arrange the whole body weight, age, sex, body fat, sensitivity and acute insulin response as hepatic insulin sensitivity risk of type-2 diabetes decline. It shows the direct involvement. It has an immense potential role to increase the hepatic gluconeogenesis or inflammation in the pathogenesity of the type-2 diabetes. As the author determined that higher ALT level regards the more risk towards the type-2 diabetes.

Diabetes Phenomenon over Elevated LFTs

Salmele et al studied based on the clinical findings of 175 unselected diabetes outpatients in Firland it has direct dissemination of LFTs abnormalities [10]. 118 patients were took up & found to have type -2 diabetes and 57 marked for type-1 diabetes. Out of 118 patients only 33 patients of type-2 diabetes used insulin in addition to diets and oral hypoglycemic drugs including metformin & sulfonylurea. Hemoglobin A_{1c} (A1c) averaged 11.2% ± 2.4%. None of the patients had clinical signification for diabetic nephropathy (diabetic kidney disease) and chronic liver disease. LFTs clinical assessments included the albumin, ALT, ALT, AP, GGT, serum concentration of cholic acid, total bilirubin and chenodeoxycholic acid. 175 diabetes outpatients (100 subject) it regard 57% from the total abnormalities corresponds to LFT, 27% (48 subject) with two abnormalities. The type-2 diabetic patients more frequently had elevated ALT (22.9 Vs 5.3%) & GGT (23.7 Vs 10.5%) level than those with type-1 diabetes.

Type-1 diabetes patients more frequently observe the elevated bilirubin level (21.1 Vs 10.2%). The increased LFTs level is more than the twice of upper limit of normal

range. The most significant variation associated with ALT & GGT. The analysis shows that the BMI >25 kg/m2 and poor diabetic control (fasting blood glucose >216 mg/dl). As ALT elevated if directly linked with the onset of diabetic since last 4 years. Use of proper diet or sulfonylurea is given on the mature onset of diabetes (35-51 years). Examine the massiveness of LFTs estimate all the histological changes, Salmela et al studies looked up for 72 sequential diabetes inpatients with hepatomegaly or abnormal LFTs as patients who were awaiting liver biopsy [10]. The type-2 diabetes patients are 68 and 4 had type-1 diabetes, but all of them had abnormal LFTs and hepatomegalay. All have normal blood counts, serum, electrolytes & renal functions. But no case reported for the heart failure. Only 5 of them had a history of social drinking alcohol and rest 67 as abstainers. 63 patients had abnormal liver histology. 48 had liver fatty liver or steatosis with non-specific inflammatory changes. 14 evidence of fibrosis reported. GGT & ALT it seems too elevated generally but here is no significant difference in mean values of ALT & GGT. The histopathology worsened (steatosis to inflammation to fibrosis). Abnormal LFTs result is common in diabetes & particularly in over weight type-2 diabetic patients. Further there is no creditability for histological changes in the liver. Erbey et al in a large group study it analysed 18,825 non-institutionalized patients with an oversampling of Mexican Americans & African Americans [11]. Total sample study in which 4.1% elevated ALT, 6.7% type-2 diabetic patients out of which 7.8% had the elevated ALT and rest 3.8% prevalence in those free from any type of diabetes. The propagation in the ALT elevation level when greater by 3 times than the normal value & have no significance difference between diabetic & non-diabetic patients (0.4 Vs 0.7%) and for the obese (BMI >30 kg/m2) & for over weight (BMI >25-30 kg/m2). They had more elevation in ALT. 10.6% prevalence in obese diabetic versm a 6.6 prevalance in obese non-diabetic patients.

Type-2 Diabetic: NAFLD

NAFLD (non-alcoholic fatty liver disease), it is the most common reason for the elevation of LFT s level in type-2 diabetic patients. In clinicopathological investigation NAFLD represent a broad spectrum of histological evidence from hepatic streatosis or fat accumulation in hepatocytes without any inflammation, to hepatic steaotsis with a necro-inflammatory component that may or

may not have fibrosis or NASH. Low or absence of alcohol consumption characterized as NAFLD with or without necro-inflammatory activities shows the macrovesicular steatosis & cast off the other forms of liver disease. Indecipherable the pathogenesis & it marked by the deposition of triglycerides within the hepatocytes. For the triglycerides deposition insulin resistance play a major role. As inflammation followed by the ATP depolarization, mitochondrial dysfunction, FA, excess intercellular & oxidant stress [3]. NAFLD is regared as the most common in patients with having elevation of serum aminotransferase ranges from mild to moderate. There is no direct intensification accordance to the histology of liver as transaminase elevation in NAFLD [12].

Non- Diabetic: NAFLD

Diabetic and non-diabetic chronic elevated LFTs in the United States is one the most effective etiology as NAFLD is replacing alcohol & viral hepatitis [3]. Among all the patients reported NAFLD, 60-95% are obese, 28-55% type-2 diabetes & 20-92% have hyperlipidemia. Further study conducted were 1,124 adults examine and they shows the evaluation of chronic elevated LFTs. Based on absence of serum markers for infection (hepatitis B & C), 81 were rectify with undetermined etiology or hereditary cause of liver disease (α-1-antitrypsin, iron, ferritin, iron binding capacity, ceruloplasmin etc) metabolic (TSH- thyroid stimulating hormone), autoimmune (anti-smooth muscle antibody, anti-mitochondrial antibody, electrophoresis, serum protein) [13]. No history reported by the chronic liver disease & non for alcohol or hepatotoxic drugs. No sarcoid in chest X-rays for all the patients. There is no evidence in article for the transaminites like celiac disease, renal insufficiency and muscle disorder. With no identified etiology of elevated liver enzymes 81 patients marked negative, abnormal history in 73 patients, all had some association to steatosis. The patient has some association to steatosis. The prevalence rate of stratosis is 50.6% & steatohepatitis is 32% but without any clarified etiology for liver disease.

With diabetes and without diabetes for individuals, same study conducted for 354 patients, to investigate abnormal LFTs over liver biopsy underwent. Steatosis and steatphepatosis on biopsy evidence excluded 66% of the patients for specific diagnosis, since their serological & clinical reports available [14].

Type-2 Diabetic and HCV Projection

In united state, predictor of type-2 diabetes is known to be independent and the most alarming cause for liver disease is hepatitis C- virus (HCV), without cirrhosis it is the most common endocrine disease within diabetic patients with high prevalence for HCV reported [15], [16]. Risk factor of acquiring HCV when comparing 176 diabetic patients to 6172 blood donors matched & it shows higher prevalence of HCV infection, diabetic patients (11.5 Vs 2.5% $p<0.001$) [17]. 72.3% had abnormal elevated LFTs, with HCV diabetic patients on comparing it with diabetic patients with no report of HCV ($p< 0.001$) it shows 27.7% impact. The study gives us the idea about screening is important for HCV among all the diabetic patients with elevated LFTs.

Elevated Transaminases Type-2 Diabetes with Statin

It not show any significant association with the heart protection study of 20,536 who has the higher risk individuals of vascular disease among all diabetes patients. The elevated rates for ALT are 2 times the upper limit of normal range were 1.8% in simvastatin group & 16% in the placebo group in the pravastation in Elderly Individuals at risk of vascular disease (PROSPER) trial, ALT or AST level is more than 3 times the upper limit of normal range of one patients in placebro group & in pravastatin only one patients reported rhabdomyoloysis [18], [19]. In pravastatin 36 patients had myalgias, compared it with placebo group only found 32 patients. Association of high dose statin therapy with more frequent abnormalities of LFTs patients with clinical cardiovascular disease (CVD) were randomized to 10-80 mg of atovastatin while treating to new targets (TNTs) trail thrice the upper limit of the normal range obtained for the incidence of persistent elevation in AST & ALT or both observe for 4-10 days and range obtained is 1.2 and 0.2% respectively ($p< 0.0001$) [20]. Recommendation based on the current large trails from the American College of physicians for type-2 diabetic patients with cardiovascular risk factors also in order to avoid any other severe disease. In major issues such as macro-vascular complication statin used as primary prevention. Routine monitoring of LFT not required in these patients, even the statins and other drugs should be avoided until the baseline abnormalities found in LFTs & myopathy as it can increase the other adverse situation too [21]. It should be advised not to use the advance statin therapy as long as patients are

monitored carefully, as for diabetic patients the baseline transaminase less than three times the upper normal limit. But there is disagreement over monitoring recurrence of these patients. Other disagreement builds on elevation of statin hepatotoxicity whether it developed by transaminase or not? [22]. The proven benefits from CVD risk reduction is less weighted over the known potential risk of statin therapy by the major possibilities of hepatotoxicity, among the diabetic patients over age of 40 years who have a multiple cardiovascular risk factors called as CVD.

Elevated Transaminase When Type-2 Diabetic Patients Administrated With Oral Agents

The sequential report of hepatotoxity led Jick et al which is introduced by the insulin sensitizer in type-2 diabetic patients to analyzed the baseline risk of liver disease on oral agents other than thiazolidinediones [23]. General Practice Research database UK based researcher identified 40,190 type-2 diabetic individuals treated with oral diabetic agents, which include metformin, guar gum & sulfonylurasa in between years 1989-1996. When the oral therapy began none of the patients reported the known liver disease. During the study periods out of 605 cases only 1.5% individuals identified as new diagnosis of liver disorder, 249 (41.2%) attributed to a predisposing conditions, 186 (31%) as mild asymptotic liver enzyme abnormalities with no clinical relevant, 113 (18.7%) had a specific non drug etiology listed. The rest 57 (8.7%) are no predisposed conditions with a clinical relevant of liver disease which attribute towards the other drugs, fatty liver & unknown. An incidence of 0.002/100 person years these two cases oral antibiotic agents not to be ruled out.

Rajagopalan et al comparison in between pioglitazone v/s oral antidiabetic agents claimed date based on the incidence of liver failure in type-2 diabetic patients [24]. As report received by the pharmacy on their first antidiabetic treatment it divided into different group based on antidiabetic therapy. If the patients belong to group pioglitazone then by the help of metformin & sulfonylurea group they matched with the patients of rosiglitazone. Same characters i.e. clinical & demographic, found within the matched groups, the analysis of patients includes 4.458 similar pairs of pioglitazone v/s rosiglitazone treated patients. 1,474 pairs of pioglitazone v/s sulfonylurea treated patients & 1,137 pairs of pioglitazone v/s metformin treated patients. No patients reported increased risk of liver failure or hepatitis with duration of 2 years by

pioglitazone when it compared with the patients on other antidiabetic agents. Reversal effect of enzymes elevation with all patients was found to be elevated ALT on pioglitazone [25].

Pioglitazone is able to control the double-blind clinical effects in placebo- controls, virtual identical between patients on pioglitazone and those of placebo (0.26 v/s 0.25%), the incidence of elevated ALT values greater than 3 times the upper limit of normal. More than 6000 patients took and studied by Lebovitz et al for the individuals affected with type-2 diabetes either insulin, metformin or glyburide and rosiglitazone placebo used various dosed in double blind clinical trials. 8.5-9% in all groups since from beginning of study the mean Alc level is same [26]. For the first months at every 4 weeks of treatment & then afterwards at a interval of 6 to 12 weeks occurred for the screening, baseline and proper measurement of liver enzymes. If any individuals found to have grater ALT, ALP or AST level by two and half times the upper limit of normal during screening then the individuals excluded from the study. This added with present recommendation when advise not to use rosiglitazone orpiglitazone. Approximate 3800 for at least 6 months, 2800 for one year & 1000 for at least 2 years monitored of all those on rosiglitazone. Among 5,006 patients who went with rosiglitazone none of them had hepatotoxic effects. ALT is thrice the upper limit of normal ranges & rosiglitazone is 0.32 %, placebo group 0.17% and 0.40 % either with insulin or sulfonyureamet formin groups. No difference found for the treatment of placebo, rosiglitazone and other antihpyerglycemic agents as study conducted a respective incidence rates of 0.29, 0.59 & 0.64/ 100 person- years had been reported. As study further proceded 5.6% of individuals whose serum ALT values in between 1- 1.5 the upper limit of normal baselone, the individuals 66% normalized ALT treated with antihyperglycemic medicines & that of only 38.7% normalized ALT they were treated by placebo normalized [26].

Over & over again found mild chronic elevation of tranaminities in diabetic patients reduced by improvised insulin resistance & it has specific support among insulin resistance, hepatic function & glycemic control.

A surrogate, thiadolidinediones for the insulin resistance use to treat NASH it was shown in pilot studies that the decrease in LFTs illustrated with rosiglitazone & pioglitazone therapy for diabetic patients.

For 48 weeks a study took placed 18 non-diabetic patients with NASH on pioglitazone with a daily dose of 30 mg/48 weeks [27]. 72% with normalized and rest all patients with decrease serum ALT level by the end of study it was observed. A great fall found in report of serum ALT level from an average of 99 units/ l to a baseline of 40 unit/l within a interval of 48 weeks.

One more study used rosigitazone for 48 weeks treatment on 30 patients with NASH a daily dose of 4 mg & impairment of glucose tolerance or diabetes among 50% of them [28]. A significant improvement were noticed in the level of mean serum ALT levels among 25 patients who finished the study of period 48 weeks with a changed notice from baseline 104 units/l to 42 units/l. Again increased in level of liver enzyme near to pretreatment for rosiglitazone found after 24 weeks offs & this observation made over the end of 72 weeks.

CONCLUSION

The elevated ALT is most common abnormalities among diabetic patients. It concluded that the individual those who having the type-2 diabetes follow the higher incidence of LFT abnormalities than the person who do not have diabetes. After proper clinical observation for more than six months if any mild chronic elevation of ALT or elevation of ALT≤ 250 unit/l in any diabetic patients found then the screening for treatable cause of chronic liver disease like hepatitis B, hepatitis C and hemochromatosis seems to have incidence in type 2 diabetes. The diagnostic workup is probably not required for those patients who do not have any evidence for more serious liver disease, such as elevation in bilirubin or prothrombin time or decrease in albumin or even in a patients who have any direct medical history & physical examination do not raise suspicion of other cause of elevated LFTs. If patients develop any preliminary symptoms which enhance the hepatic impairment before administering drug therapy, a proper routine monitoring of LFTs in patients with type 2 diabetes it requires. Time to time screening based on the clinical assessments. So, nod your head that transaminases does not always have correlate with the histological changes in the liver. As higher glucose level achieved then descends in level of ALT shown by antidiabetic agents. If elevation of ALT is more than three times the upper limit of normal range then it would not be an antipathy to start any oral antidiabetic or lipid modifying therapy.

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